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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,845	12/20/2001	Thomas Backenfeld	PLOVIN-5	1446

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EXAMINER	
LEWIS, PATRICK T	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,845	BACKENFELD ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25,28-31,37 and 39-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25,28-31,37 and 39-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Applicant's Response dated November 4, 2003

2. In the Response filed November 4, 2003, claims 1-24, 26-27, 32-36, and 38 were canceled; claims 25, 37, and 42 were amended; and claims 48-67 were added. Applicant presented arguments directed to the rejection of claims 8-9, 26-27, and 37-46 under 35 U.S.C. 112, second paragraph and the rejection of claims 1-34 under 35 U.S.C. 103(a). Claims 25, 28-31, 37, and 39-67 are pending. An action on the merits of claims 25, 28-31, 37, and 39-67 is contained herein below.

3. The rejection of claim 1-13 and 22 under the judicially created doctrine of obviousness-type double patenting has been rendered moot in view of the amendment dated November 4, 2003.

4. The objection to claims 10-13 has been rendered moot in view of the amendment dated November 4, 2003.

5. The rejection of claims 8-9 and 26-27 has been rendered moot in view of the amendment dated November 4, 2003.

6. The rejection of claim 37-46 under 35 U.S.C. 112, second paragraph is maintained for the reasons of record as set forth in the Office Action dated July 3, 2003.

7. The rejection of claims 1-24, 26-27, and 32-34 under 35 U.S.C. 103(a) has been rendered moot in view of the amendment dated November 4, 2003.

8. The rejection of claims 25 and 28-31 under 35 U.S.C § 103(a), is maintained for the reasons of record set forth in the Office Action dated July 3, 2003.

Objections/Rejections of Record Set For the in Office Action dated July 3, 2003

9. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

10. Claims 37-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "granulation conditions" has not been described in such a way as to apprise one of ordinary skill in the art of the parameters under which the granulation process occurs. In the absence of clear recitation of active methodological steps, it is impossible for the skilled artisan to practice the instantly claimed invention.

11. Applicant argues that it should be apparent that "granulation conditions" are conditions which allow the granulating step to occur. The examiner respectfully disagrees. The "granulation conditions" are seen to be of critical importance in the practice of the instantly claimed method as there is seen to be a direct correlation between the "granulation conditions" and the stability of the final product.

12. Claims 25 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backensfeld et al. U.S. Patent 5,798,338 (Backenfeld) in combination with Parikh

et al. U.S. Patent 6,228,399 (Parikh), Pitha U.S. Patent 4,596,795 (Pitha), Krattenmacher *Contraception* (**2000**), vol. *62*, pages 29-38 (Krattenmacher)

Claim 25 is drawn to a composition comprising an estrogen and a cyclodextrin and one or more excipients, the composition having a stability such that said estrogen is in an amount of at least 85% w/w in relation to the initial content of said estrogen after storage for 12 months at a temperature between 40 °C and 75% relative humidity. Claims 28-31 depend from claim 25. Claim 28-29 limit the amount of estrogen in the formulation. Claims 30-31 limit the amount of estrogen and the cyclodextrin.

Backensfeld teaches compositions comprising an inclusion complex of ethinyl estradiol and β-cyclodextrin (column 1, lines 27-46; column 3, lines 16-27; claim 6). The complex can be processed into the desired dosage forms, such as tablets, powder, granulates, etc. after the addition of the commonly used additives, such as, lactose, starch, polyvinylpyrrolidone, magnesium stearate, and preservatives (column 2, lines 44-49). Backenfeld teaches the ratio of cyclodextrin to sex hormone in the complex as 1:1, 2:1, 3:1, 3:2 or 1:2 (column 2, lines 50-61). Backenfeld further teaches that the complex is dried in a vacuum with phosphorous pentoxide (column 3, lines 5-11).

Backensfeld differs from the instantly claimed invention in that Backensfeld does not teach: 1) the relative humidity of the composition or 2) the long-term stability of the complex. However, these deficiencies are taught by the prior art and would have been obvious to one of ordinary skill in the art at the time of the invention.

Pitha teaches the administration of a combination of sex hormones, particularly testosterone, progesterone and estradiol in the form of their inclusion complexes with a

cyclodextrin as an oral contraceptive and for the treatment of premenstrual tension syndrome (FIG 1; column 3 lines 39-44; column 1, lines 52-57; FIG. 3-4; column 4, lines 1-25).

Krattenmacher teaches that drospirenone is a progestogen having a pharmacological profile closely related to progesterone, especially with regard to antimineralocorticoid and antiandrogenic activities (page 29, column 2, second paragraph). Krattenmacher also teaches that adverse effects related to other oral contraceptives may be decreased using drospirenone and that contraceptive efficacy and adverse effects of drospirenone/ethinyl estradiol combination treatment have been evaluated with favorable results.

Parikh teaches that microparticles (particles having diameters of from nanometers to micrometers) provide some specific advantages over the unformulated non-micronized drug particles (column 1, lines 32-47). The advantages include improved oral bioavailability of drugs that are poorly absorbed from GI tract, development of injectable formulations that are currently available only in oral dosage form, less toxic injectable formulations that are currently prepared with organic solvents, sustained release of intramuscular injectable drugs that are currently administered through daily injection or constant infusion, and preparation of inhaled, ophthalmic formulation of drugs that otherwise could not be formulated for nasal or ocular use.

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition/formulation comprising a complex between an estrogen and a cyclodextrin as instantly claimed in view of the prior art. Although

Backesnfeld is silent on the relative humidity of the composition/formulation, it does teach drying the complex under vacuum with phosphorous pentoxide. One of ordinary skill in the art would expect the composition, when dried, to have a relative humidity less than 40%. In regards to the long-term stability of the composition/formulation, Backensfeld teaches drying the complex and applicant states on page 15 of the instant disclosure that the relative humidity of the composition/formulation is the most important factor relating to stability. Thus, the dried composition/formulation is seen to meet the stability limitations of the instantly claimed invention. Since the Office does not have the facilities for preparing the claimed materials and comparing when with prior art inventions, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. One of ordinary skill in the art at the time of the invention would be motivated to make said modifications in order to reduce the steroidal dosages used. This in turn would lead to a reduction in side effects

13. Applicant argues that 1) Backensfield does not teach the required PVP content and 2) Backensfield does not teach compositions meeting the stability requirement. Applicant also makes mention to method claims that were not part of the rejection and arguments directed to inherency. No claims drawn to methods were rejected in the Office Action dated July 3, 2003. No rejections under 35 U.S.C. 102 have been set forth on the record. As such, these remarks are not seen as germane.

Applicant's arguments directed to stability requirement have been fully considered but are not persuasive. The examiner disagrees with applicant's assertion that the data for tablets A and E in table 1.3 of Example 1 shows a side-by-side

comparison. As shown in Table 1.1 of Example 1, tablet A contains PVP while tablet E does not. Furthermore, the data presented in Table 1.3 is confusing. The examiner assumes that the numbers cited on the table are the content (%) of ethinyl estradiol (EE) recovered at the start, after 3 months at 40 °C or 60 °C wherein RH = 75%, and after 12 months at 25 °C wherein RH = 60% or at 40 °C wherein RH = 75%. It is noted that the maximum amount of EE in tablet A that could be recovered is only 93.1% while tablet E contains more EE than is theoretically possible (>103%) at time = 0. Backensfeld teaches drying the complex, and applicant states on page 15 of the instant disclosure that the relative humidity of the composition/formulation is the most important factor relating to stability. The examiner further disagrees with applicant's assertion that Backensfeld teaches compositions comprising about 4.9% w/w of PVP. As shown in Example 3, the w/w % of PVP <<2% (2.750 mg PVP / 55,000 mg tablet). In the absence of some proof of a secondary nature to obviate the rejection as set forth in the Office Action dated July 3, 2003, or of some specific limitations which would tip the scale of patentability in the favor of the instantly claimed invention, the instantly claimed composition is indeed *prima facie* obvious.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 56-59 and 63-67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 56-59, claim 56 depends from claim 56 rendering claim 56 and subsequent dependent claims indefinite.

Regarding claims 63-67, the term "granulation conditions" has not been described in such a way as to apprise one of ordinary skill in the art of the parameters under which the granulation process occurs. In the absence of clear recitation of active methodological steps, it is impossible for the skilled artisan to practice the instantly claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. Claims 47-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Backensfeld et al. U.S. Patent 5,798,338 (Backenfeld) in combination with Parikh et al. U.S. Patent 6,228,399 (Parikh), Pitha U.S. Patent 4,596,795 (Pitha), Krattenmacher *Contraception* (**2000**), vol. *62*, pages 29-38 (Krattenmacher), and Simmons U.S. Patent 4,154,820 (Simmons).

Claim 25 is drawn to a composition comprising an estrogen and a cyclodextrin and one or more excipients, the composition having a stability such that said estrogen is in an amount of at least 85% w/w in relation to the initial content of said estrogen after storage for 12 months at a temperature between 40 °C and 75% relative humidity. Claims 26-34 depend from claim 25. Claims 47-62 depend from claim 25. Claim 47 limits the amount of PVP in the composition. Claim 48 limits the excipients. Claims 49-50 limit the estrogen. Claims 51-52 limit the cyclodextrin. Claim 53 limits the cyclodextrin/estrogen ratio. Claims 54-59 and 61 further comprise one or more therapeutically active agents. Claims 60 and 62 limit the particle size of the preparation.

Backensfeld teaches compositions comprising an inclusion complex of ethinyl estradiol and β-cyclodextrin (column 1, lines 27-46; column 3, lines 16-27; claim 6). The complex can be processed into the desired dosage forms, such as tablets, powder, granulates, etc. after the addition of the commonly used additives, such as, lactose, starch, polyvinylpyrrolidone, magnesium stearate, and preservatives (column 2, lines 44-49). Backenfeld teaches the ratio of cyclodextrin to sex hormone in the complex as 1:1, 2:1, 3:1, 3:2 or 1:2 (column 2, lines 50-61). Backenfeld further teaches that the complex is dried in a vacuum with phosphorous pentoxide (column 3, lines 5-11).

Backensfeld differs from the instantly claimed invention in that Backensfeld does not teach: 1) the relative humidity of the composition, 2) compositions comprising one or more additional active agents, 3) micronized formulations, 4) long-term stability of the complex, nor 5) compositions containing an antioxidant. However, these deficiencies are taught by the prior art and would have been obvious to one of ordinary skill in the art at the time of the invention.

Pitha teaches the administration of a combination of sex hormones, particularly testosterone, progesterone and estradiol in the form of their inclusion complexes with a cyclodextrin as an oral contraceptive and for the treatment of premenstrual tension syndrome (FIG 1; column 3 lines 39-44; column 1, lines 52-57; FIG. 3-4; column 4, lines 1-25).

Krattenmacher teaches that drospirenone is a progestogen having a pharmacological profile closely related to progesterone, especially with regard to antimineralocorticoid and antiandrogenic activities (page 29, column 2, second

paragraph). Krattenmacher also teaches that adverse effects related to other oral contraceptives may be decreased using drospirenone and that contraceptive efficacy and adverse effects of drospirenone/ethinyl estradiol combination treatment have been evaluated with favorable results.

Parikh teaches that microparticles (particles having diameters of from nanometers to micrometers) provide some specific advantages over the unformulated non-micronized drug particles (column 1, lines 32-47). The advantages include improved oral bioavailability of drugs that are poorly absorbed from GI tract, development of injectable formulations that are currently available only in oral dosage form, less toxic injectable formulations that are currently prepared with organic solvents, sustained release of intramuscular injectable drugs that are currently administered through daily injection or constant infusion, and preparation of inhaled, ophthalmic formulation of drugs that otherwise could not be formulated for nasal or ocular use.

Simmons teaches estrogen compositions wherein antioxidants are used to stabilize estrogen (column 4, lines 32-67).

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition/formulation comprising a complex between an estrogen and a cyclodextrin as instantly claimed in view of the prior art. Although Backesnfeld is silent on the relative humidity of the composition/formulation, it does teach drying the complex under vacuum with phosphorous pentoxide. One of ordinary skill in the art would expect the composition, when dried, to have a relative humidity less than 40%. It would have also been obvious to one of ordinary skill to complex a

combination of an estrogen and a progestogen as Pitha teaches such. Although Pitha does not teach drospirenone, it would have been obvious to substitute drospirenone for progesterone in the inclusion complex as Krattenmacher teaches that drospirenone is a progestogen having a pharmacological profile closely related to progesterone, especially with regard to antimineralocorticoid and antiandrogenic activities. The skilled artisan would expect a reasonable degree of success in substituting one member of a group for another since both members have similar therapeutic activity. The combination of varying ratios of drospirenone and cyclodextrin is seen to be within the purview of the skilled artisan. It would have also been obvious to employ one or more antioxidants in the composition to provide added stability as taught by Simmons.

In regards to the long-term stability of the composition/formulation, Backensfeld teaches drying the complex and applicant states on page 15 of the instant disclosure that the relative humidity of the composition/formulation is the most important factor relating to stability. Thus, the dried composition/formulation is seen to meet the stability limitations of the instantly claimed invention. Since the Office does not have the facilities for preparing the claimed materials and comparing when with prior art inventions, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art. One of ordinary skill in the art at the time of the invention would be motivated to make said modifications in order to reduce the steroidal dosages used. This in turn would lead to a reduction in side effects

Conclusion

20. Claims 25, 28-31, 37, and 39-67 are pending. Claims 25, 28-31, 37, and 39-67 are rejected. No claims are allowed.

21. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 703-305-4043. The examiner can normally be reached on M-F 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 703-308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Patrick T. Lewis, PhD
Examiner
Art Unit 1623

James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

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February 6, 2004